DEPARTMENT OF HEALTH & HUMAN SERVICES

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Food and Drug Administration
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Re: Docket No. 1999P-1654/PSA1 & SUP1

Dear Mr. Mahinka and Ms. Sanzo:

This responds to your petition for stay of action dated May 26, 1999 (Petition), and supplement to that petition dated November 15, 2001 (Supplement), submitted on behalf of Zeneca Inc. (Zeneca), now AstraZeneca Pharmaceuticals LP (AstraZeneca). In your petition, you ask the Food and Drug Administration (FDA) to stay the effective date of any pending, tentative, or final approval of an abbreviated new drug application (ANDA) submitted by Bedford Laboratories (Bedford) seeking approval of a generic[1] version of Diprivan (propofol) Injectable Emulsion (Diprivan) and deny the ANDA because it should not be approved under section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355(j)) and FDA regulations (21 CFR parts 314 and 320).

After carefully considering your petition and supplement, we deny your requests for the reasons stated below.

I. BACKGROUND

On October 2, 1989, FDA approved Zeneca's new drug application (NDA) for Diprivan (propofol) injectable emulsion.[2] Propofol is a nonnarcotic, nonbarbiturate, anesthetic agent indicated for induction and maintenance of anesthesia, for monitored anesthesia, and for support of mechanical ventilation and sedation in the adult intensive care unit (ICU).[3]

After Zeneca introduced Diprivan in the United States, FDA, the Centers for Disease Control and

[1] For purposes of this response, the term *generic* refers to new drug products for which approval is sought in an ANDA submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355(j)).
[2] AstraZeneca is the holder of the approved NDA (19-627) for Diprivan.
[3] See approved product labeling for Diprivan (propofol) Injectable Emulsion. Propofol is not approved for induction of anesthesia in patients younger than 3 years of age or for maintenance of anesthesia in patients younger than 2 months of age because its safety and effectiveness have not been established in those populations. Propofol is not approved for support of mechanical ventilation or sedation in pediatric ICU patients.

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Prevention (CDC), and Zeneca became aware of postoperative fevers and infections in clusters of patients to whom Diprivan was administered. Investigators ultimately determined that these adverse effects resulted from microbial contamination caused by mishandling of Diprivan by medical personnel. Despite a change in Diprivan's education programs and the dissemination of "Dear Doctor" letters, the rate and number of infections were not adequately diminished. At FDA's direction, Zeneca sought alternative solutions to this problem. Subsequently, Zeneca reformulated the drug product and submitted a supplemental NDA for approval of the new formulation of Diprivan. The new formulation contained the excipient disodium edetate (EDTA) for the purpose of preventing microbial infections. Because Zeneca was required to conduct clinical studies to obtain approval of the supplemental NDA, Zeneca requested, and we granted, a 3-year period of exclusivity for the formulation of propofol with EDTA. This exclusivity period expired June 11, 1999.[4]

Thereafter, Bedford submitted an ANDA seeking approval of a generic version of Diprivan injectable emulsion. In its ANDA, Bedford proposed to substitute 0.1 percent benzyl alcohol, which is a preservative or antimicrobial agent, for EDTA in its propofol injectable emulsion product.

II. DISCUSSION OF ISSUES

You cite several reasons why you believe that we cannot approve Bedford's ANDA for a benzyl alcohol-containing propofol product. As discussed below, we disagree with your conclusion on each of these matters.

A. Benzyl Alcohol Is Not an Active Ingredient in Bedford's Generic Formulation of Propofol.

You state that benzyl alcohol is an active ingredient in Bedford's propofol product because it is pharmacologically active as an anesthetic agent. You therefore argue that because Diprivan does not contain benzyl alcohol, Diprivan and Bedford's product do not contain the same active ingredients (Petition at 9-10). Consequently, you maintain that we must refuse to approve Bedford's ANDA under § 314.127(a)(3)(ii), which provides that FDA will refuse to approve an ANDA when the applicant submits information insufficient to show that the active ingredients are the same as those of the reference listed drug (for a reference listed drug with more than one active ingredient). You contend that Bedford is, in effect, attempting to use an ANDA rather than an NDA to obtain approval of a combination drug product.

Depending on its concentration in a drug product, benzyl alcohol may be either a preservative or an active ingredient. As you note, benzyl alcohol 1 to 4 percent is an active ingredient when used as a local anesthetic in anorectal drug products for over-the-counter human use as described in the regulations (21 CFR 346.10(b)). However, at lower concentrations, such as that present in

[4] Zeneca received a 3-year period of exclusivity for a new indication for Diprivan on February 20, 2001. This exclusivity expired on February 20, 2004. Zeneca also received pediatric exclusivity for Diprivan.

Bedford's propofol product (0.1 percent), it is regarded as a preservative (see section II.B of this response). You have not presented, and we are not aware of, any scientific data that support your statement that benzyl alcohol when administered intravenously is pharmacologically active as an anesthetic agent or otherwise augments or increases anesthetic activity. Therefore, benzyl alcohol is not an active ingredient in Bedford's propofol product. Because the benzyl alcohol in Bedford's product does not constitute an active ingredient that differs from the active ingredient in Diprivan, the presence of benzyl alcohol in Bedford's product does not bar the approval of the product under § 314.127(a)(3). Because the benzyl alcohol in Bedford's propofol product is not an active ingredient but a preservative, this product is not a fixed-combination drug product under 21 CFR 300.50 (a combination of two or more drugs in a single dosage form). Bedford's submission of an ANDA for its propofol product is appropriate.

Further, we may approve Bedford's ANDA for propofol because, under the Act (sections 505(j)(2)(A)(ii)(I) and 505(j)(4)(C)(i)) and FDA regulations (§§ 314.92(a)(1) and 314.127(a)(3)(i)), Bedford's ANDA provides sufficient information to show, among other things, that the active ingredient (i.e., propofol) contained in its generic propofol product is the same as that contained in the reference listed drug, AstraZeneca's Diprivan.

B. EDTA Is a Preservative in Diprivan.

You claim that the EDTA in Diprivan is not a preservative because EDTA does not meet the definition of a preservative in the *United States Pharmacopeia (USP)* and because Diprivan's labeling states that the drug product "contains no preservative." You note that under § 314.94(a)(9)(iii), for ANDAs referencing parenteral drug products, the only differences in excipients that may be approved by FDA are those involving an antioxidant, a preservative, or a buffer. Therefore, you maintain that because EDTA is not a preservative, antioxidant, or buffer, FDA's regulations (§ 314.127(a)(8)(ii)(B)) prohibit Bedford from substituting benzyl alcohol for EDTA (Petition at 10).

We disagree with your conclusion because, among other reasons, the EDTA in Diprivan does meet the *USP* definition of a preservative as well as the definition of preservative in other authoritative sources.[5] The *USP* defines antimicrobial preservatives as "substances added to nonsterile dosage forms to protect them from microbiological growth or from microorganisms that are introduced inadvertently during or subsequent to the manufacturing process."[6] The *USP* further states that, "[i]n the case of sterile articles packaged in multiple-dose containers, antimicrobial preservatives are added to inhibit the growth of microorganisms that may be

[5] *Remington's Pharmaceutical Sciences* states that "[a] preservative is, in the common pharmaceutical sense, a substance that prevents or inhibits microbial growth and may be added to pharmaceutical preparations for this purpose to avoid consequent spoilage of the preparations by microorganisms" (18th ed., ch. 66, p. 1286 (1990)). The *Handbook of Pharmaceutical Excipients* states that "[e]detic acid and edetates possess some antimicrobial activity but are most frequently used in combination with other antimicrobial preservatives due to their synergistic effects" (2nd ed., p. 176 (1994)).

[6] *United States Pharmacopeia (USP) 27*, <51> Antimicrobial Effectiveness Testing, at 2148.

introduced from repeatedly withdrawing individual doses."[7] The EDTA in Diprivan meets this definition because it was specifically added to prevent microbial contamination that apparently caused postoperative fevers and infections in patients to whom Diprivan was administered. Zeneca selected EDTA precisely because it "appear[ed] to provide enhanced microbial stability."[8] Although the EDTA in reformulated Diprivan is not present in a sufficient amount to meet the *USP* testing standard for effectiveness of a preservative,[9] EDTA still functions as a preservative because its primary purpose is to suppress the growth of microorganisms.[10]

Like the EDTA in Diprivan, the benzyl alcohol in Bedford's propofol product meets the USP definition of a preservative. Bedford included benzyl alcohol in its product for the same reason that Zeneca added EDTA to Diprivan.

As discussed further below, we may approve, consistent with §§ 314.94(a)(9)(iii) and 314.127(a)(8)(ii)(B), Bedford's generic version of Diprivan containing benzyl alcohol rather than EDTA as a preservative, provided the use of the different preservative does not affect the safety or efficacy of the drug product.

C. The Use of a Warning Does Not Bar a Finding That a Difference in Preservatives Does Not Affect Safety.

You state that under § 314.94(a)(9)(iii), the proponent of a generic version of a parenteral drug must establish that the differences between the generic drug and the reference listed drug do not affect the safety of the proposed drug product. You state that our regulations provide no exception to this requirement or the prohibition under § 314.127(a)(8)(ii)(B) against approving an ANDA when the requirement is not met. You maintain that, in particular, additional warnings in the generic product's labeling may not be used to avoid finding that the differences affect safety (Petition at 11). For the reasons stated below, these regulations do not prohibit approval of a proposed generic product whose labeling includes a warning (or, as in this case, cautionary statements) about a preservative that differs from that of the reference listed drug.

The Act (section 505(j)(4)(H)) provides that FDA must approve an ANDA unless:

> information submitted in the [ANDA] or any other information available to the Secretary shows that (i) the inactive ingredients of the drug are unsafe for use under the conditions

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[7] Id.

[8] David Goodale, DDS, Ph.D., Zeneca, Inc., Anesthetic and Life Support Drugs Advisory Committee Transcript, p. 15 (June 10, 1995).

[9] *USP 27*, <51> Antimicrobial Effectiveness Testing, at 2150.

[10] Further, at least one district court noted that the Agency's determination (i.e., that a particular inactive ingredient was a preservative) was consistent with the "[c]ontains no preservatives" statement in the labeling. See *Zeneca, Inc. v. Shalala*, 1999 U.S. Dist. LEXIS 12327, at *22-*23 (Aug. 11, 1999), *aff'd*, 213 F.3d 161 (4th Cir. 2000). The court noted that "[t]he use of the word 'preservative' in the context of approval of a generic drug relates to the *function* of the inactive ingredient in the formulation. In the labeling requirement, the word refers to the *effectiveness* of the antimicrobial agent." Id.

> prescribed, recommended, or suggested in the labeling proposed for the drug, or (ii) the composition of the drug is unsafe under such conditions because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included.

Likewise, the implementing regulations at § 314.127(a)(8)(i)(A) and (a)(8)(i)(B) permit FDA to refuse to approve an ANDA when:

> [i]nformation submitted in the [ANDA or] any other information available to FDA shows that . . . [t]he inactive ingredients . . . are unsafe for use . . . or [t]he composition of the drug product is unsafe, . . . under the conditions prescribed, recommended, or suggested in the proposed labeling because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included.

Pertinent regulations on preservatives in parenteral drug products are set forth in §§ 314.94(a)(9)(iii) and 314.127(a)(8)(ii)(B). Section 314.94(a)(9)(iii) states:

> Generally, a drug product intended for parenteral use shall contain the same inactive ingredients and in the same concentration as the reference listed drug identified by the applicant. . . . However, an applicant may seek approval of a drug product that differs from the reference listed drug in preservative, buffer, or antioxidant provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

The corresponding provision in § 314.127(a)(8)(ii)(B) provides that:

> FDA will consider an active ingredient in, or the composition of, a drug product intended for parenteral use to be unsafe and will refuse to approve the [ANDA] unless it contains the same inactive ingredients, other than preservatives, buffers, antioxidants, in the same concentration as the listed drug, and if it differs from the listed drug in a preservative, buffer, or antioxidant, the application contains sufficient information to demonstrate that the difference does not affect the safety or efficacy of the drug product.

Bedford's generic propofol has the same inactive ingredients as those contained in Diprivan except that Bedford's generic propofol contains a different preservative (i.e., benzyl alcohol) than that contained in Diprivan (i.e., EDTA). This difference is clearly permitted under the regulations provided that the difference does not affect the safety or efficacy of the drug product. Under § 314.127(a)(8)(ii)(A), FDA can determine whether a change in an inactive ingredient may adversely affect a drug product's safety or efficacy based on "its experience with reviewing inactive ingredients, and from other information available to it." As discussed in section II.E of this response, we found that sufficient information was available in Bedford's ANDA and other information before us to conclude that Bedford's use of benzyl alcohol as a preservative did not affect the safety and efficacy of the drug product.

Your assertion that §§ 314.94(a)(9)(iii) and 314.127(a)(8)(ii)(B) prohibit the use of a warning to

address safety concerns related to the use of a different preservative in a generic drug was rejected in *Zeneca v. Shalala*, 213 F.3d 161 (4th Cir. 2000). In *Zeneca*, the Fourth Circuit upheld FDA's conclusion that these regulations are broad enough to permit the use of warning statements to obviate any potential risks from a different preservative. *Zeneca* involved a challenge to FDA's approval of a generic version of the same drug product at issue here—Diprivan. In January 1999, we approved an ANDA for a generic version of Diprivan submitted by Gensia Sicor Pharmaceuticals, Inc. (Gensia). We determined that the sodium metabisulfite (Sulfite) that Gensia used in its propofol product (instead of the EDTA in Diprivan) did not affect the safety profile of the drug. However, we required labeling statements to alert practitioners to the potential for allergic reactions due to the presence of sulfites.

Zeneca filed suit against FDA, maintaining that the substitution of Sulfite for EDTA raised safety concerns and required a warning label that was impermissible under §§ 314.94(a)(9)(iii) and 314.127(a)(8)(ii)(B). We argued that Zeneca's interpretation of the regulations was unreasonably narrow. We referred to the plain language of section 505(j)(4)(H) of the Act (the statute that the two regulations were issued to implement), which expressly provides that under the ANDA process, our consideration of the safety of inactive ingredients of generic drugs is dependent on (1) the "conditions prescribed, recommended, or suggested in the labeling" and (2) the "type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included." The district court granted our motion for summary judgment.[11] The Fourth Circuit affirmed, finding that (1) the language of §§ 314.94(a)(9)(iii) and 314.127(a)(8)(ii)(B) was broad enough to encompass our interpretation and (2) our interpretation was consistent with the statute (*Zeneca*, 213 F.3d at 168).

In accordance with *Zeneca*, the regulations (i.e., §§ 314.94(a)(9)(iii) and 314.127(a)(8)(ii)(B)) do not prohibit us from approving Bedford's propofol product with a preservative different from the one in Diprivan solely because the labeling for Bedford's product contains, in this case, cautionary statements related to the presence of benzyl alcohol in the formulation. Similar to *Zeneca*, it is reasonable for us to conclude that, although Bedford's propofol formulation justifies a cautionary statement for benzyl alcohol with respect to pediatric patients, the safety and efficacy of the product are not affected because both Bedford's propofol product and Diprivan are safe and effective when used under the conditions prescribed, recommended, or suggested in the labeling. The statements in Bedford's propofol labeling are sufficient to alert practitioners and other health care providers to any potential risks to pediatric patients due to the presence of benzyl alcohol.

[11] The district court concurred with Gensia stating that "'FDA reasonably concluded that, although the product has a different risk profile, requiring a warning for sulfite sensitive patients, the safety of the product was not affected because both Gensia Sicor's product and Diprivan are safe when used as directed'" (*Zeneca*, 1999 U.S. Dist. LEXIS 12327, at *29-*30).

D. Clinical Studies Are Not Routinely Required to Demonstrate That Use of a Different Preservative Does Not Affect the Safety or Efficacy of a Parenteral Drug Product.

You state that there are significant differences between the antimicrobial additive EDTA in Diprivan and the antimicrobial additive benzyl alcohol in Bedford's generic propofol. You also state that substitution of benzyl alcohol for EDTA is a change in an ingredient other than a preservative and raises serious safety, toxicology, formulation, and product stability questions. You therefore maintain that the substitution of benzyl alcohol for EDTA necessitates that Bedford submit preclinical, clinical, and other substantive data confirming the safety and efficacy of its product (Petition at 12).

The Act and FDA regulations do not routinely require submission of clinical studies on safety and efficacy for approval of an ANDA for a parenteral product with a change in preservative. We approved Bedford's propofol product consistent with the Act (e.g., section 505(j)(4)(H)) and FDA regulations (e.g., § 314.127(a)(8)(i)(A) and (B) and (a)(8)(ii)(B)). That is, Bedford's generic propofol has the same inactive ingredients as those contained in Diprivan except that Bedford's generic propofol contains a different preservative (i.e., benzyl alcohol) than that contained in Diprivan (i.e., EDTA). As noted above, this is a difference clearly permitted under the Act and regulations provided that the difference does not affect the safety or effectiveness of the product.

As stated in section II.C of this response, we concluded, in accordance with § 314.127(a)(8)(ii)(A) and on the basis of information in Bedford's ANDA and other information before the Agency, that Bedford's use of benzyl alcohol as a preservative did not affect the safety and efficacy of the drug product. Therefore, we did not require Bedford to conduct clinical studies to demonstrate the safety and effectiveness of its propofol product formulated with benzyl alcohol rather than EDTA.[12]

E. The Available Data Do Not Establish Any Significant Safety or Efficacy Concerns Associated with Benzyl Alcohol in Bedford's Propofol Product.

You state that the use of benzyl alcohol in propofol injectable emulsion, especially in concentrations that you allege appear necessary to ensure antimicrobial protection comparable to Diprivan, raises unique safety concerns due to what you refer to as documented problems associated with adverse allergic or toxic reactions, the potential for increased potency of dangerous endotoxins, the potential for altered efficacy, and the body's inability to metabolize large amounts of benzyl alcohol. You also state that a low concentration of benzyl alcohol decreases antimicrobial effectiveness and the safety of the drug by failing to protect against

[12] See also FDA's January 4, 1999, response (at 5-7) to the April 7, 1998, petition for stay of action (Docket No. 98P-0221/PSA1) submitted by Zeneca for the Agency's rationale for requiring clinical studies for the approval of Zeneca's Diprivan formulated with EDTA.

certain organisms (Petition at 12-13). As explained below, FDA concludes that the available data do not support your claims about safety and efficacy concerns associated with the use of benzyl alcohol in a propofol drug product.

1. Gasping Syndrome and Benzyl Alcohol Toxicity

You state that the administration of solutions containing benzyl alcohol to neonates has resulted in "gasping syndrome," a condition that causes gasping, metabolic acidosis, liver failure, and a significant drop in white cell and platelet counts, and often results in death. You state that, by contrast, Diprivan has been used extensively and safely with neonates and pediatric patients. You maintain that the administration of a large volume of benzyl alcohol into the body continuously and over an extended period of time may cause toxicity due to the body's ability or inability to metabolize the alcohol. You also suggest that the effects of benzyl alcohol poisoning may be more pronounced and more dangerous in the critically ill patients who will receive Bedford's propofol product. In sum, you conclude that Bedford's product may present serious risks of toxicity due to the particular dosage of benzyl alcohol that will be administered (Petition at 13-14).

We do not share your conclusions about the risk of gasping syndrome associated with the use of benzyl alcohol in propofol. Dr. J. Gershanik first described gasping syndrome in a report published initially in 1981 in *Clinical Research* and later in 1982 in the *New England Journal of Medicine*. Dr. Gershanik described the syndrome as one of multiple organ system deterioration and eventual death.[13] These two reports contained a retrospective comparative analysis that recounted 20 deaths of low-birth-weight infants in two centers from 1981 to 1982. All of the deaths were attributed to the use of benzyl alcohol as a preservative in solutions used to flush catheters, dilute medications, and deliver aerosol treatments.

As a result of a growing awareness of the toxicity problems, FDA, the U.S. Pharmacopeial Convention (USPC), and drug manufacturers took a number of steps to highlight the hazards of using benzyl-alcohol-containing products in newborns. In May 1982, FDA urged pediatricians and hospital personnel to stop using all fluids containing benzyl alcohol as flush or diluent solutions in infants.[14] In June 1982, we met with all known manufacturers of bacteriostatic water for injection and bacteriostatic sodium chloride injection and with staff from the USPC. At that meeting, manufacturers of these classes of products voluntarily agreed to place a warning on product labels against the use of the products in newborns. After

[13] Gershanik, J.J., et al., "The Gasping Syndrome and Benzyl Alcohol Poisoning," *New England Journal of Medicine*, 307:1384-1388, 1982.

[14] On May 28, 1982, FDA sent 22,000 letters to hospital pharmacists, 19,000 letters to pediatricians, and 8,400 letters to hospital administrators notifying them of the potential for toxicity associated with benzyl alcohol. We also prepared warning notices for inclusion in bulletins of the American Society of Hospital Pharmacists and the American Nurses Association and other professional associations. In addition, we prepared a press release dated June 1, 1982, that urged pediatricians and other hospital personnel not to use fluids preserved with benzyl alcohol (or other antimicrobial agents) as intravascular flush solutions for newborn infants and not to use diluents with this preservative to reconstitute or dilute medications for infants (see 54 FR 49772 at 49773, December 1, 1989).

the meeting, the USPC revised *USP* monographs for these classes of products to bear the warning "Not for use in newborns."[15] In 1985, the Agency published a notice of intent entitled "Parenteral Drug Products Containing Benzyl Alcohol or Other Antimicrobial Preservatives" (50 FR 20233, May 15, 1985). In the notice, we solicited data, information, and comments on the issues raised, and specifically asked for recommendations on any further course of action.

In 1989, we withdrew our notice of intent to propose, among other things, a cautionary labeling requirement for multidose parenteral drug products with benzyl alcohol because we had received no reports of benzyl alcohol-related toxicity since 1982 (54 FR 49772). We stated that the steps taken by the Agency, drug manufacturers, and the USPC may have helped reduce the use of benzyl alcohol products for newborns during this period. As a result of these initiatives and the lack of adverse reports, we concluded in 1989 that it was not necessary to issue either a regulation prohibiting the use of antimicrobial preservatives in single-dose containers of parenteral solutions or a regulation requiring cautionary labeling of multiple-dose parenteral drug products containing benzyl alcohol or other antimicrobial preservatives (54 FR 49772 at 49773).

The American Academy of Pediatrics had released a statement in September 1983 expressing concern about the use of benzyl alcohol in neonates but also pointing out that there were no controlled studies to confirm the hypothesis linking benzyl alcohol use with the gasping syndrome. The consensus was that "for newborn infants, it may be preferable to avoid use of medications with preservatives whenever possible; however, the presence of benzyl alcohol as a preservative should not proscribe use of medications indicated for treatment of an infant."[16] In a 1997 policy statement, the Academy concluded that "the toxic effects in newborns relate primarily to the use of preservative containing flush solutions, which clearly are to be avoided in newborns. At low doses, such as those present when medications preserved with benzyl alcohol are administered, benzyl alcohol is safe for newborns."[17] Retrospective studies have now demonstrated a significant decline in mortality and other adverse events after discontinuation of use of a benzyl alcohol-containing solution to flush intravascular catheters or reconstitution of drugs for delivery through these catheters in the newborn population.[18]

We have reviewed, based on our scientific experience and expertise, the potential hazards associated with benzyl alcohol. A review of all relevant information (including medical literature, adverse event reports, and post-marketing experience with drug products containing benzyl alcohol) indicates that a generic propofol product containing benzyl alcohol presents negligible risk to the indicated patient population. This information provides, among other things, evidence of the safe use of a number of parenteral products containing benzyl alcohol already on the market. As of 1996, over 50 parenteral formulations had already been approved

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[15] *USP 20*, Supp. 4, May 1983.

[16] American Academy of Pediatrics (AAP), Committee on Fetus and Newborns, Committee on Drugs, "Benzyl Alcohol: Toxic Agent in Neonatal Units," *Pediatrics*, 72(3):356-358, 1983.

[17] AAP, "'Inactive' Ingredients in Pharmaceutical Products: Update (Subject Review)," pp. 268-278, January 1997.

[18] Id.

with benzyl alcohol.[19] These drugs include erythromycin, procainamide, heparin, midazolam, trimethoprim/sulfamethoxazole, and clindamycin. Many of these products are given to the same patient populations and in the same clinical settings as propofol and are also given over an extended period of time either by infusion or intermittent dosing.[20] More than half of these drug products contain a higher concentration of benzyl alcohol than Bedford's product.

A comparison between Bedford's generic propofol and Versed[21] (midazolam hydrochloride), another parenteral drug containing benzyl alcohol, supports the safety of benzyl alcohol in the Bedford product. When 1 milligram (mg)/milliliter (mL) of Versed (1 percent benzyl alcohol) is used for maintenance of sedation, it is possible that as much as 28.8 mg of benzyl alcohol/kilogram (kg)/day could be administered.[22] Bedford's propofol formulation would normally be expected to deliver only up to 7.2 mg of benzyl alcohol/kg/day.[23] Thus, the level of benzyl alcohol that potentially could be delivered with Bedford's generic propofol formulation is within the range already demonstrated to be safe by clinical experience with approved products. We also note that Versed was approved for use in neonates (zero to 2 months) for continuous infusion in intensive care settings, which would permit continuous exposure over days. Propofol is approved only for short-term indications in pediatric patients (i.e., it is not approved for infusion in the intensive care setting in any pediatric age group). Furthermore, propofol is not approved for *any* indication in pediatric patients younger than 2 months of age. Based in part on clinical experience with labeled and unlabeled use of benzyl alcohol-containing products such as Versed, we expect that Bedford's proposed propofol product will be safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling.

A review of the medical literature and other information available to the Agency also suggests that a generic propofol product containing benzyl alcohol presents negligible risk to the indicated patient population. In his research of gasping syndrome, Gershanik states:

> Infants with gasping syndrome received average daily quantities of benzyl alcohol, in the form of a bacteriostatic sodium chloride and bacteriostatic water flush, of 99 to 234 mg per kilogram of body weight before the onset of gasping. A matched control group, consisting of eight infants who received solutions containing benzyl alcohol as a

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[19] FDA Inactive Ingredient Guide, Division of Drug Information Resources, Center for Drug Evaluation and Research, FDA (January 1996); *USP Pharmacopeial Forum*, 22:2696-2704, 1996.

[20] The only reports of benzyl alcohol related toxicity have occurred in neonates in conjunction with multiple IV flushes of bacteriostatic saline or water (see footnote 5).

[21] We note that Versed Injection appears on the "Discontinued Drug Product List" of the *Approved Drug Products With Therapeutic Equivalence Evaluations* (*Orange Book*) (24th ed., 2004, at 6-85). The "Discontinued Drug Product List" identifies drug products that have been discontinued from marketing for reasons other than safety or effectiveness (see 68 FR 46645, August 6, 2003). There are generic versions of Versed that are currently marketed, and some of those products contain benzyl alcohol.

[22] See approved product labeling.

[23] Bedford's generic propofol contains a 1 mg/mL concentration of benzyl alcohol, which delivers up to 7.2 mg/kg/day, assuming a 50 mcg/kg/min infusion (the highest usual recommended rate for ICU sedation of adults). Propofol is not approved for ICU or monitored anesthesia care sedation in any pediatric age group (i.e., the indications for which these calculations are most pertinent). Propofol is not approved for any indication in neonates.

> preservative, but did not have the gasping syndrome, received solutions containing benzyl alcohol of 27 to 99 mg per kilogram over the same period.[24]

The amount of benzyl alcohol that could be administered with Bedford's propofol at its highest usual recommended infusion rate for sedation is 7.2 mg/kg of body weight per day, well below the toxic levels of >99 mg/kg/day in Gershanik's study. It should also be noted that the neonates in Gershanik's study were administered bolus doses in a catheter flush, whereas Bedford's propofol is administered as a slow parenteral infusion. Based on this comparison, we determined that a generic propofol formulation with benzyl alcohol is safe for use under the conditions prescribed, recommended, or suggested in the labeling.

In addition, we conducted a search of adverse events associated with the use of parenteral products containing benzyl alcohol in three specific pediatric age groups, including neonates. We selected the following products (all with higher benzyl alcohol concentrations than Bedford's generic propofol) for the search: Versed injection (10 mg/mL benzyl alcohol), Ativan injection (20 mg/mL benzyl alcohol), Valium injection (15 mg/mL benzyl alcohol), Nuromax injection (9 mg/mL benzyl alcohol), Norcuron for injection (9 mg/mL benzyl alcohol), and Tracrium (9 mg/mL benzyl alcohol). The three different age groups included zero to 1 month, 1 month to 2 years, and 2 years to 6 years. Particular attention was paid to the first group (neonates) because this was the group in which the toxic syndrome from benzyl alcohol was observed and described in 1981-1982. Review of all 58 reports for neonates revealed no evidence of benzyl alcohol toxicity. Review of adverse events in the other two age groups also revealed no apparent cases of benzyl alcohol toxicity.

2. Anesthetic Activity

You state that the combination of two anesthetics in Bedford's formulation (benzyl alcohol and propofol) likely will affect the efficacy of the propofol. You maintain that without knowledge of how and to what degree the addition of benzyl alcohol changes the efficacy of propofol, it is not possible to determine the proper dosage of Bedford's formulation compared to the dosage of Diprivan (Petition at 15).

We have found no evidence that benzyl alcohol will increase anesthetic activity in Bedford's propofol product. Inherent anesthetic action of benzyl alcohol when administered intravenously is neither supported nor refuted in the literature.[25] Moreover, the literature contains no evidence that benzyl alcohol produces a sedative or hypnotic effect in the levels present in currently marketed products that contain benzyl alcohol at higher concentrations than Bedford's propofol product.

Any possible additive or synergistic anesthetic effect would presumably be due to the ability of

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[24] See Gershanik, footnote 5.

[25] Some references indicate a possible local anesthetic effect of benzyl alcohol, but no references indicate that benzyl alcohol has a general anesthetic effect.

benzyl alcohol to produce central nervous system (CNS) depression, which could act in concert with the desired pharmacologic effect of propofol. However, a published study of benzyl alcohol administration in dogs after intravenous sodium pentothal administration suggests otherwise. In the study, dogs that received doses of 9 to 45 mg of benzyl alcohol directly into the CNS via intrathecal injection displayed the same degree of anesthesia as those that did not receive the benzyl alcohol.[26] Thus, in this animal study, benzyl alcohol did not appear to have any meaningful CNS depressant activity, even when high doses were injected directly into the CNS.

3. Bacterial Endotoxins

You state that benzyl alcohol has been found to increase the morbidity and/or mortality associated with bacterial endotoxins. You maintain that the health of any patient with, or at risk of, an infection could be further compromised by the introduction of benzyl alcohol into that patient's system due to the likelihood that benzyl alcohol will exacerbate an infection or reduce the patient's ability to stave off an infection (Petition at 16).

We found only one published study that appears to indicate that combining benzyl alcohol with a bacterial endotoxin may increase the morbidity and mortality associated with the endotoxin.[27] However, in this 1984 study, rats were exposed to 40 mg of benzyl alcohol, an amount that far exceeds the predicted exposure of benzyl alcohol delivered in Bedford's 7.2 mg/kg/day daily dosage. A review of the literature identified no further studies on this topic. Therefore, it would not be reasonable for us to conclude that benzyl alcohol causes potentiation of endotoxins.

4. Neurotoxicity and Hypersensitivity Reactions

You state that benzyl alcohol raises certain neurotoxicity and hypersensitivity safety concerns (Petition at 16-17). Although progressive central neurotoxicity does occur with toxic doses of benzyl alcohol, these toxicities likely could occur only with exposure to higher amounts of benzyl alcohol than the amount present in Bedford's dosage of its propofol product. Also, any resultant toxic effects from benzyl alcohol would not be isolated but rather would be a component of a syndrome involving multisystem failure. We have not found reports that implicate intravenous administration of formulations containing benzyl alcohol at the dosage levels in Bedford's propofol product in the causation of neurotoxicity. Similarly, we have found no evidence of an increased incidence of hypersensitivity reactions related to approved drug products containing benzyl alcohol. Consequently, hypersensitivity reactions do not appear to be a particular concern with Bedford's propofol product.

5. Antimicrobial Effectiveness and Benzyl Alcohol

You state that for a propofol product with benzyl alcohol to have at least the same antimicrobial

[26] DeLand, G.H., "Intrathecal Toxicity Studies with Benzyl Alcohol," *Applied Pharmacology*, 25:153-156, 1973.
[27] Cebula, T.A., A.N. El-Hage, and V.J. Ferrans, "Toxic Interactions of Benzyl Alcohol with Bacterial Endotoxins." *Infection and Immunity*, 44:91-96, 1984.

effectiveness as Diprivan, the dosage would exceed World Health Organization (WHO) maximum daily dosage amounts and would produce significant toxicities. You maintain that available data show that benzyl alcohol may fail to prevent or inhibit microbial growth in propofol injectable emulsion when it is added to the drug in concentrations below 0.1 percent. You also maintain that benzyl alcohol is only moderately active against gram negative bacteria and thus will fail to protect patients against such bacteria (Petition at 14-15, 17).

The WHO has established the acceptable daily intake of benzyl alcohol of 0-5 mg/kg body weight.[28] However, this recommendation applies to the chronic intake of benzoic acid/sodium benzoate through the consumption of food; it is not applicable to short-term exposure to benzyl alcohol through the intravenous administration of drug products. With respect to toxicity, as we stated earlier, the available clinical data do not demonstrate a significant risk of toxicity in the neonatal population (see section II.E.1). As to benzyl alcohol's activity against gram negative bacteria, Bedford has demonstrated the bacteriostatic nature of its propofol product against a panel of microorganisms, including gram negative bacteria *E. coli* and *P. aeruginosa*. The data that Bedford provided indicate that the effectiveness of its product in preventing bacterial growth over the labeled period of use is not significantly different than that of Diprivan.

You maintain that to ensure that benzyl alcohol prevents microbial growth as well as Diprivan, Bedford's product must be tested for antimicrobial efficacy in its final, marketed form, over the range of pH at which the drug is expected to be distributed and used (which you state should be based on Diprivan's pH levels from 7.0 to 8.5) (Petition at 18).

Under section 505(j)(4)(A) of the Act, the Agency must approve an ANDA unless, among other things, the methods used in, or the facilities, and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve the identity, strength, quality, and purity. Implementing regulations set forth a parallel provision at § 314.127(a)(1). We have reviewed data establishing that pH specifications of propofol products may be adjusted to achieve the desired antimicrobial effect without altering product characteristics, such as stability. The pH range of Bedford's propofol product happens to be the same as that of Diprivan, 7.0 to 8.5. Further, we determined that for Bedford's generic propofol, the methods used in, or the facilities, and controls used for, the manufacture, processing, and packing of the drug are adequate to assure and preserve the identity, strength, quality, and purity.

6. Stability and Compatibility Issues

You state that Diprivan is a highly complex emulsion drug and that minor modifications to an emulsion system can seriously affect the stability and integrity of the emulsion system. Accordingly, you state that we must carefully evaluate whether Bedford's product is safe and effective as manufactured, particularly if the pH differs from Diprivan. You further maintain that benzyl alcohol can accelerate the autoxidation of fats and therefore affect the stability and

[28] "Toxicological Evaluation of Certain Food Additives," WHO Food Additive Series 37 (1996), Annex 4.

emulsion in Bedford's formulation, which might lead to the formulation of free fatty acids. You maintain that large oil globules could form that would pose a significant health and safety risk, particularly to critically ill patients (Petition at 19-20).

As stated in section II.E.5 of this response, the pH level in Bedford's propofol product is the same as that of Diprivan and, in any case, pH specifications of propofol can be adjusted to achieve the desired antimicrobial effects without adversely affecting stability and other important product characteristics.

With respect to your claim regarding oil globules, we have reviewed data comparing globule-size distribution among Diprivan and other propofol injectable emulsions. The data show that there tends to be significant variation in globule size among lots of these products due to slight changes in manufacturing processes. Therefore, globule size is not a significant factor in determining the pharmaceutical equivalency[29] or safety of a propofol product as long as the globule size is within an acceptable range.

You state that a generic propofol applicant must provide data establishing the compatibility of the proposed antimicrobial additive with packaging and administration materials and substances and with all other components of the formulation. You maintain that the final formulation should be tested in the primary container intended to be used in marketing for the product's shelf life (24 months) at up to 30° C. You also state that Bedford should repeatedly challenge the packaged product with inoculations of a range of microbes to assure constancy of antimicrobial activity. In addition, you state that the compatibility of the product with the components of the administration materials should be assured by challenging the final formulation after being drawn into syringes of various manufacturers. Finally, you maintain that Bedford should be required to show the compatibility of its product with other commonly used intravenous infusion fluids (Petition at 21).

As stated above, Bedford has provided sufficient data establishing that the methods used in, and the facilities, and controls used for, the manufacture, processing, and packing of Bedford's generic propofol product are adequate to assure and preserve the identity, strength, quality, and purity of the drug. This includes data on packaging and administration materials. Typically, FDA review of stability studies for a proposed product includes an evaluation of antimicrobial compatibility through effectiveness testing and/or chemical analysis for preservative content.[30] When chemical analysis is used, the acceptance criterion is based on microbial testing to determine effective levels of the preservative. This addresses interaction of the antimicrobial

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[29] Pharmaceutical equivalents are "drug products in identical dosage forms that contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety...; do not necessarily contain the same inactive ingredients; and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates" (21 CFR 320.1(c)).

[30] See *Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics* (February 1987), at 12.

with the packaging container material and other components of the formulation, and it also addresses the stability of the overall formulation.

We agree that the stability studies on a proposed product should be conducted in the container intended for marketing. However, for ANDA approval, stability studies may be conducted under accelerated conditions, i.e., 3 months at 40° C, rather than 24 months at 30° C.[31]

We disagree with your position that Bedford should repeatedly challenge its product with a range of microbes. Such repeated challenges are not appropriate with a single-dose product like Bedford's propofol product. *USP* <51> Antimicrobial Effectiveness Testing specifies a single inoculation of separate test vials with individual challenge organisms, followed by enumeration of the challenge organisms over time.

We disagree with your position that the compatibility of Bedford's product with the administration materials should be assured by challenging the final formulation after being drawn into syringes of various manufacturers. The syringes used for drug delivery and the materials of construction for syringes are generally selected for their inertness and negligible interaction with other substances. We also disagree with your position that Bedford should be required to perform extensive testing on the compatibility of its product with other intravenous infusion fluids. As noted above, we determined during the ANDA review process that the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are adequate to assure and preserve the identity, strength, quality, and purity of the drug product. Further, Bedford's product labeling would contain substantially the same statements as those in the Diprivan labeling with respect to compatibility. There is no evidence to suggest, nor do we expect, that there would be compatibility issues unique to Bedford's product.

F. FDA Will Not Reject Bedford's ANDA Because the Labeling for the Generic Propofol Product Differs From That of Diprivan.

You state that section 505(j)(2)(A)(v) of the Act and § 314.94(a)(8)(iv) prohibit the use of a warning label in a drug submitted for approval pursuant to an ANDA if the reference listed drug does not also contain that warning (Petition at 22-24).

Consistent with the Act, FDA regulations, and case law, Bedford's generic propofol containing benzyl alcohol would have the same labeling as Diprivan except for differences permitted by law. The Act requires the ANDA applicant to show that "the labeling proposed for the new [generic] drug is the same as the labeling approved for the listed drug. . .except for changes required because of differences approved under a petition filed under [section 505(j)(2)(C) of the Act] or because the new drug and the listed drug are produced or distributed by different manufacturers" (section 505(j)(2)(A)(v) of the Act; *see also* section 505(j)(4)(G) of the Act).

[31] Id. at 43.

FDA regulations similarly require, under § 314.94(a)(8)(iv), that the "[l]abeling . . . proposed for the [generic] drug product must be the same as the labeling approved for the reference listed drug, except for changes required because of differences approved under a petition filed under § 314.93 *or because the drug product and the reference listed drug are produced or distributed by different manufacturers*" (emphasis added).[32] Section 314.94(a)(8)(iv) then lists examples of permissible differences in labeling that may result because the generic drug product and reference listed drug product are produced or distributed by different manufacturers. Such examples include differences in expiration date, formulation, bioavailability, pharmacokinetics, and labeling revisions made to comply with current FDA labeling guidelines or other guidance.

Bedford's generic propofol containing benzyl alcohol has a different formulation than AstraZeneca's Diprivan containing EDTA. Under the Act and FDA regulations, Bedford's generic propofol labeling may differ from AstraZeneca's Diprivan labeling to reflect differences in formulation (i.e., the change in preservative). Labeling revisions may also be made to comply with current FDA labeling regulations (e.g., 21 CFR 201.56 and 201.57).

Although you acknowledge the above-stated statutory and regulatory framework, you nonetheless maintain that the addition of a benzyl alcohol related warning not present in Diprivan would require FDA to reject Bedford's ANDA (Petition at 24). You rely primarily on a statement in FDA's 1989 proposed rule on ANDA regulations, in which we said that we would not approve a generic drug "where a proposed change in a generic drug . . . would jeopardize the safe or effective use of the product so as to necessitate the addition of significant new labeled warnings. . . ." (Petition at 23, quoting 54 FR 28872 at 28884 (July 10, 1989)).

Our decision regarding inclusion in Bedford's labeling of a benzyl alcohol-related cautionary statement would not conflict with this preamble statement (which we note relates specifically to warnings). We made clear in the proposed rule that differences in labeling relating to warnings are permissible by noting that an innovator drug's label "might differ" from the generic drug label because of the presence of Yellow No. 5 (54 FR 28872 at 28884). In the 1992 final rule on ANDA regulations, we referred to the possibility that a generic drug's labeling might contain warnings not present in the innovator drug's labeling when we stated that we would "carefully review" labeling differences involving warnings (57 FR 17950 at 17953 (April 28, 1992)). Further, the presence of benzyl alcohol in Bedford's propofol product is not a change that "would jeopardize the safe or effective use of the product" (54 FR 28872 at 28884). We have concluded that Bedford's generic propofol containing benzyl alcohol can be safely and effectively used under the conditions recommended or suggested in the labeling. We have also concluded that the benzyl alcohol-related statements included in Bedford's labeling are adequate to protect against potential inappropriate use of Bedford's product.

The Fourth Circuit upheld our position regarding labeling differences and warnings in *Zeneca*

[32] *See generally Zeneca*, 1999 U.S. Dist. LEXIS 12327.

(discussed in section II.C of this response). In *Zeneca*, we had concluded that the sulfite warning for Gensia's generic version of propofol was within the exceptions to the same-labeling requirement in § 314.94(a)(8)(iv) for (1) formulation differences and (2) differences required to comply with current FDA labeling guidelines.[33] Zeneca argued that the generic drug's labeling may only reflect differences in the components or ingredients of the drug, not safety risks associated with the components or ingredients.

The Court of Appeals found that the sulfite safety warning in Gensia's labeling was a direct result of the difference in formulation between Gensia's propofol with sulfite and Diprivan. Because a difference in preservative is a permitted variation in formulation under § 314.94(a)(9)(iii), the court found that it was reasonable for FDA to interpret its own regulation to allow corresponding differences in labeling to identify the preservative and provide any appropriate warnings (213 F.3d at 169). Similarly, the labeling of Bedford's generic propofol product may include precautions related to the use of benzyl alcohol as a preservative rather than the EDTA in Diprivan. Bedford's propofol labeling will be sufficient to alert practitioners of any potential risks associated with benzyl alcohol with respect to pediatric patients.

G. The Regulations Do Not Require Bedford to Provide Evidence Demonstrating In Vivo Bioequivalence to Diprivan.

You state that Bedford must show that its formulation containing benzyl alcohol is bioequivalent to Diprivan, such that it does not significantly differ from Diprivan in the rate and extent of delivery of propofol. You further state that FDA may not waive the requirement for evidence of in vivo bioavailability and bioequivalence for Bedford's propofol product under § 320.22(b)(1)(i) and (ii) because propofol is a parenteral emulsion, rather than a parenteral solution, and contains an inactive ingredient (benzyl alcohol) that differs from the inactive ingredients in Diprivan (Petition at 25-26).

Generally, under the Act (section 505(j)(2)(A)(iv)), an ANDA must contain information to show that the generic drug is bioequivalent to the reference listed drug. Under § 320.21(b), an ANDA must contain either (1) evidence of bioequivalence of the ANDA product to the reference listed drug or (2) information showing bioequivalence that is sufficient to allow the FDA to waive the submission of evidence demonstrating in vivo bioequivalence as described in the regulations. Under § 320.21(e), evidence demonstrating the in vivo bioequivalence of a drug product can be obtained using one of the approaches set forth in § 320.24. Section 320.24(b) lists several approaches for determining in vivo bioequivalence, including in vivo and in vitro tests and, under § 320.24(b)(6), any other approach that FDA deems adequate to establish bioequivalence.

We agree that it would not have been appropriate to waive the in vivo evidence requirement under § 320.22(b)(1) because that provision applies to parenteral solutions intended for administration by injection and propofol is an injectable emulsion. An emulsion is a dispersed

[33] Under 21 CFR 201.22, package inserts for prescription drugs containing sulfites must include a warning statement because sulfites may cause allergic-type reactions in certain susceptible persons.

system containing at least two immiscible liquid phases. One of these phases is dispersed as globules within the other phase. A third component, an emulsifying agent, is added to the system to improve its stability. Emulsions may provide a useful way to deliver poorly water-soluble drugs via parenteral routes. The poorly water-soluble drug is in solution in the non-water phase of the emulsion. Two emulsions with similar composition and physical characteristics are expected to deliver the dissolved drug to the patient at the same rate and extent.

Accordingly, we ask any applicant for a generic propofol injectable emulsion product to provide the following: (1) formulation data, (2) data comparing the globule size distribution profiles of the generic product and Diprivan, and (3) data comparing propofol partitioning in the oily and aqueous phases of the generic product and Diprivan. If two propofol injectable emulsion products have the same active ingredients, inactive ingredients (except for differences permitted under FDA regulations), globule size distribution, and propofol partitioning, bioequivalence is assured because the drug is already in solution in products with equivalent physical properties and is therefore available for absorption into the body at the same rate and extent. Therefore, requiring ANDA applicants to meet these criteria is an appropriate approach to establishing bioequivalence under §§ 320.21(b)(1) and 320.24(b)(6). Based on data that Bedford submitted, we concluded that (1) Bedford's product and Diprivan have the same active ingredients and inactive ingredients (except for differences in the latter permitted by regulation), (2) the globule size distribution of the two products is not significantly different, and (3) propofol partitioning in the oil and aqueous phases is not significantly different in both products. We therefore concluded that Bedford's product is bioequivalent to Diprivan.

H. Bedford's Generic Propofol Product Is Therapeutically Equivalent to Diprivan.

You maintain that although FDA evaluates bioequivalence based primarily on active ingredients and EDTA would be classified as inactive, the underlying premise for therapeutic equivalence (i.e., the comparison of ingredients for similar clinical and function effects) requires the Agency to compare the safety profile of the inactive ingredients in Bedford's product with those in Diprivan. You state that a comparison between EDTA and benzyl alcohol will mandate an FDA conclusion that Bedford's product is not therapeutically equivalent to Diprivan because benzyl alcohol has been linked to severe adverse reactions not associated with EDTA (Petition at 29).

Drug products are regarded as therapeutical equivalents if they are pharmaceutical equivalents and they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.[34] As discussed elsewhere in this response, we have concluded, based on our review of the available evidence, that the benzyl alcohol in Bedford's propofol product is unlikely to pose a significant safety risk to patients when administered in accordance with product labeling. Consequently, the safety profile of Bedford's product provides no basis for concluding that the product is not therapeutically equivalent to

[34] *Orange Book* at viii.

Diprivan.

I. The Issue of Market Exclusivity for Diprivan Is Moot.

You state that the approval of Bedford's ANDA would be contrary to section 505(j)(5)(D)(iv) of the Act because the approval would result in the loss of market exclusivity granted to Zeneca when FDA approved the supplemental NDA for the reformulation of Diprivan with EDTA (Petition at 31-33). This issue is moot because all exclusivity for the reformulated Diprivan has expired.

J. A Generic Formulation of Propofol With Benzyl Alcohol Will Not Present Unnecessary Risks to Pediatric Patients.

You state that evidence suggests that there has been significant off-label use of propofol in pediatric patients. You suggest that, given Diprivan's new indication for use in maintenance of anesthesia for patients as young as 2 months of age, there is a high probability that approval of a propofol formulation with benzyl alcohol would result in exposure of these patients to potentially unsafe levels of benzyl alcohol. Therefore, you maintain that FDA should take into account the adverse consequences of the benzyl alcohol additive in a generic propofol formulation if it were used off-label in a pediatric population (Supplement at 2-3).

As is the case for all drugs, there is the potential for off-label use of Diprivan and any generic propofol formulation. We do not interfere with physicians' judgments about off-label uses of approved drugs. We will address any potential risks to the pediatric population, including neonates, in the labeling of any generic propofol formulation containing benzyl alcohol.

K. FDA Has No Evidence That a Generic Propofol Formulation Containing Benzyl Alcohol Presents Significant Morbidity or Mortality Risks to African-American Patients.

You state that new medical literature and supportive references suggest that propofol with benzyl alcohol may present safety risks to individuals with an allelic variant of alcohol dehydrogenase enzyme (ADH2*3) that predisposes them to decreased clearance of alcohol. You further state that in the African-American population, this form of enzyme is expressed to a 20 percent degree, which can result in increased serum concentrations of benzyl alcohol that have been associated with increased toxicity. You suggest that for those African-Americans affected by ADH2*3 enzyme deficiencies who are administered propofol with benzyl alcohol in anesthesia, benzyl alcohol could accumulate in the body from all sources, leading to toxicity and possibly death (Supplement at 3-4).

You have not provided, and we are unaware of, any evidence of adverse events resulting from the administration of anesthetics with benzyl alcohol in the African-American or any other population with an allelic variant of alcohol dehydrogenase enzyme. As stated in section II.E.1

of this response, there are many approved products with benzyl alcohol given to the same patient population and in the same clinical setting as propofol and given over an extended period of time. As of this date, we have not received any reports of the adverse events you describe concerning the use of benzyl alcohol during induction and maintenance of anesthesia.

L. The AB Rating for Generic Propofol Is Appropriate, and Differences Between Bedford's Generic Propofol and Diprivan Are Adequately Conveyed in the Labeling.

You state that the safety warnings on currently marketed generic propofol with sodium metabisulfite are not effectively communicated (Supplement at 4-7). You also maintain that the AB rating of this product (indicating bioequivalence to the reference listed drug, Diprivan) has resulted in published references that contain no safety warning, use of generic propofol in at least one patient at risk for sulfite-related reactions, and other misunderstandings by physicians who assume that generic propofol and Diprivan are interchangeable in all patients (id. at 4-5). Therefore, you state that (1) FDA should consider that attempts to communicate warnings for generic propofol with benzyl alcohol will not be effective and (2) giving the drug an AB rating will weaken the safety warnings associated with benzyl alcohol because the rating will provide a basis for the routine substitution of the drug for Diprivan (id. at 7-8).

As stated in section II.H of this response, drug products are considered to be therapeutically equivalent only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. We have reviewed the safety and clinical data on Bedford's generic propofol product and have determined that Bedford's product and Diprivan are therapeutically equivalent. We will require any generic propofol drug product containing benzyl alcohol to include in its labeling appropriate statements pertaining to the presence of benzyl alcohol in the formulation. The *Orange Book* (at vii) specifically states that "FDA considers drug products to be therapeutically equivalent . . . even though they may differ in certain other characteristics such as . . . excipients (including . . . preservatives). . . . When such differences are important in the care of a particular patient, it may be appropriate for the prescribing physician to require that a particular brand be dispensed as a medical necessity." Health care practitioners are responsible for applying their professional judgment and reading the labels of drug products before making generic substitutions and should be entrusted to do so.[35] As the district court stated in *Zeneca*, "[t]o assume that health care providers would either fail to read or ignore clear warnings would call into question th[e] entire [statutory] scheme" (*Zeneca*, 1999 U.S. Dist. LEXIS 12327, at *30). Thus, the AB rating for Bedford's propofol product is appropriate, and the differences between that product and Diprivan are adequately conveyed in the labeling.

[35] *See also Bristol-Meyers Squibb Co. v. Shalala*, 91 F.3d 1493 (D.C. Cir. 1996) (noting that FDA "does not regulate. . .possible substitution of a generic drug for the pioneer by doctors or pharmacists"); *Sigma-Tau Pharmaceuticals, Inc. v. Schwetz*, 288 F.3d 141, at 147 (4th Cir. 2002) (rejecting a foreseeable use theory as a bar to generic drug approvals by stating that such a theory ". . . might frustrate the longstanding practice of Congress, the FDA, and the courts not to interfere with physicians' judgments and their prescription for off-label uses").

M. A Stay of Approval of Bedford's ANDA for Generic Propofol Is Not Justified.

You state that FDA's denial of the requested stay of approval of Bedford's propofol product under 21 CFR 10.35[36] would result in irreparable injury to AstraZeneca and, potentially, harm to numerous medical centers, health care workers, and patients who rely on the long-standing safety and efficacy profile of Diprivan. You further state that denial of the stay would damage Diprivan's reputation and encourage the entry into the market of many unproven propofol formulations, resulting in a high number of adverse events due to product mishandling. You maintain that we may be unable to act on these reports without expending significant resources to determine the source of the reports because of confusion created by the generic product among health care professionals who mistakenly believe that the product is the "same as" Diprivan. You further maintain that if the stay is not granted, a product that FDA approved as safe and effective for the intended use will not be used because of the confusion, and the drop in use will result in an irreparable loss of sales of Diprivan (Petition at 34-35).

We will grant a stay only when all the provisions set forth in § 10.35(e)(1)-(4) have been satisfied. We need not address your claims that your cases are not frivolous and are being pursued in good faith and that you would otherwise suffer irreparable injury because we conclude that you have not demonstrated sound public policy grounds for a stay. Furthermore, we conclude that the potential delay resulting from the stay is outweighed by public health or other public interests.

You state that staying the approval of Bedford's ANDA for propofol with benzyl alcohol will benefit public policy goals because a stay will prevent significant safety risks to patients receiving anesthesia or sedation. You also state the public health will benefit from the exclusion of such products until adequate testing can be performed (Petition at 35).

We do not believe that any public policy or public health grounds support granting a stay to prevent the approval of Bedford's ANDA. For the reasons stated above, we believe that it is unlikely that denying the stay and approving Bedford's propofol product will result in an increase of adverse events associated with propofol (or consequent product misperception in the medical community) given the thorough safety evaluation and other safeguards that we employed in reviewing Bedford's ANDA — as we do with all ANDAs. We do not believe that approving Bedford's propofol with benzyl alcohol will result in significant harm to patients, and we will ensure that the product meets statutory and regulatory requirements for safety and effectiveness. Moreover, the approval of ANDAs for generic drug products such as Bedford's propofol is one of the Agency's important public health initiatives. The dual purpose of the Drug Price

[36] Under 21 CFR 10.35(e), FDA will grant a stay of action if the following apply:
(1) The petitioner will otherwise suffer irreparable injury;
(2) The petitioner's case is not frivolous and is being pursued in good faith;
(3) The petitioner has demonstrated sound public policy grounds supporting the stay; and
(4) The delay resulting from the stay is not outweighed by public health or other public interests.

Competition and Patent Term Restoration Act of 1984 (Public Law No. 98-417, 98 Stat. 1585), which established the ANDA process, was to expedite the availability of safe, effective, and less expensive generic versions of approved drugs while simultaneously encouraging the costly research and development efforts that lead to the discovery of therapeutically important new drugs. Consequently, a stay of the approval of Bedford's ANDA would not be in the public interest.

III. CONCLUSION

For the reasons stated above, your request that we stay the approval of Bedford's ANDA for generic propofol with benzyl alcohol is denied.

Sincerely,

Randall W. Lutter, Ph.D.
Acting Associate Commissioner
for Policy and Planning